EPA+DHA therapy reduces PMN activity in microenvironment of venous leg ulcers: A randomized, controlled study

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Transforming health, Transforming lives
Chronic venous leg ulcers

Debilitating wounds

Over 2 million people/yr.

Treatment – $15 billion
Pathobiology

- Chronic venous insufficiency
- High numbers of activated polymorphonuclear leukocytes (PMNs)
- Chronic inflammation

Eming et al. 2010. *Journal of Proteome Research.*
Pathobiology

High numbers of activated PMNs in microenvironment secreting excessive levels of damaging proteases

Serena et al., 2016. *Wound Repair and Regeneration*
Current standard care therapies

Primarily **topical** therapies

**Gold standard: compression**
Various dressings
Growth factors
Topical Solutions

Dressings to absorb excessive proteases.
Systemic approach?

To target excessive PMN activation in microcirculation and wound microenvironment.

- Micronized purified flavonoid fraction (e.g. Daflon)
- Eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA)
Metabolism of Polyunsaturated Fatty Acids

Testing Fish Oil Derivatives In Healing Of Chronic Venous Leg Ulcers

Possible actions of EPA+DHA that would support use of EPA+DHA supplementation to facilitate healing of CVLUs.
**Research study**

**Design**: Randomized, double-blind, repeated-measures

**Participants**: Men and women, ages 18-85 years with at least one existing CVLU for ≥ 3 months; prescribed compression therapy; ankle brachial pressure index ≥ 0.8; target wound of ≥ 1 x 1 inches.

**Active group** (n = 20) - EPA+DHA therapy x 8 wks

**Placebo Group** (n= 20) – Placebo therapy x 8 wks.

Testing fish oil derivatives in healing of chronic venous leg ulcers 1R21NR012803-01A1
Measures at 0, 4 and 8 weeks:

- N-6, n-3 PUFAs (blood)
- Polymorphonuclear leukocytes (PMNs) (blood, wound fluid)
- PMN-derived proteases (wound fluid)
- Wound area yet to be healed
Aim 2: Determine levels of PMN activation and PMN-derived proteases after 4 and 8 weeks of EPA+DHA therapy or placebo therapy.
Aim 3: Determine reduction in wound area at 4 and 8 weeks compared to baseline in both groups.
Results
<table>
<thead>
<tr>
<th></th>
<th>EPA+DHA* (n = 16)</th>
<th>Control* (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>60.3 (12.6)</td>
<td>60.9 (11.8)</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>10 (62.5)</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>6 (37.5)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>White (n, %)</td>
<td>12 (75)</td>
<td>14 (75)</td>
</tr>
<tr>
<td>African American (n, %)</td>
<td>4 (25)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some high school (n, %)</td>
<td>0</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>High school graduate (n, %)</td>
<td>6 (37.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Some college (n, %)</td>
<td>4 (25)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>College graduate (n, %)</td>
<td>6 (37.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>BMI, kilograms/meter² - mean (SD)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>40.4 (8.2)</td>
<td>42.7 (13.8)</td>
</tr>
<tr>
<td>28 days</td>
<td>40.9 (8.5)</td>
<td>42.7 (8.5)</td>
</tr>
<tr>
<td>56 days</td>
<td>40.6 (8.9)</td>
<td>42.1 (13.7)</td>
</tr>
<tr>
<td>Wound Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size, baseline (cm²) - mean (SD)</td>
<td>15.6 (34.4)</td>
<td>19.7 (23.2)</td>
</tr>
<tr>
<td>Estimated wound age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months (n, %)</td>
<td>8 (50)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>&gt; 6 months (n, %)</td>
<td>8 (50)</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Healed by 56 days (n, %)</td>
<td>5 (31)</td>
<td>5 (26)</td>
</tr>
</tbody>
</table>
Plasma PUFAs

(A) EPA

(B) DHA

(C) AA:EPA

(D) N6:N3

p ≤ 0.05
PMN activation in wound fluid

\[ p \leq 0.05 \]
PMN activation in wound fluid

\[ p \leq 0.05 \]
PMN-derived proteases in wound fluid
Wound healing
Clinical Relevance

EPA + DHA Supplementation?
Goal: Improve Healing Outcomes!
Team

- Sashwati Roy, PhD – OSU College of Medicine
- N. Parinandi – OSU College of Medicine
- Alai Tan, PhD – OSU College of Nursing
- OSU Clinical Research Center Staff
Future research:
Test the extent to which EPA+DHA therapy can reduce excessive PMN activation, expedite healing, AND prevent recurrence in larger cohort of CVLU patients.
THANK YOU
Questions?